

Appln. No. 09/030,061
Amd. dated October 7, 2003
Reply to Office Action of April 8, 2003

REMARKS

The Office Action and the cited and applied references have been carefully reviewed. Claims 29-33, 35, and 36 presently appear in the this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 34 and 35 have been objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of the previous claim. This objection as it relates to claim 34 is obviated by the cancellation of claim 34 without prejudice. The objection with regard to claim 35 is traversed because claim 35 does indeed further limit the subject matter of previous claim 29 as it positively recites for one or more amino acid residues inserted or one or more residues additionally removed and/or replaced that was only recited in claim 29 as being optional.

Reconsideration and withdrawal of the objection are therefore respectfully requested.

Claims 33 and 34 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendment to claim 33 and the cancellation of claim 34 without prejudice.

Claims 29-36 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Ushio et al., EP 0712931 A2, or

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Okamura et al., U.S. Patent No. 5,912,324 and further in view of Mark et al. U.S. Patent No. 4,588,585. This rejection is respectfully traversed.

The examiner states that it is well known in the art that cysteine residues in many protein molecules can be substituted or deleted without affecting biological activities of the proteins. However, this is not correct. Cysteine residues may constitute an active center of a protein even if the cysteine residues are not involved in a disulfide bond. This is shown in the following references attached hereto for the examiner's consideration:

PARSONAGE et al., *Biochemistry*, 34:435-441 (NADH Peroxidase) (1995)

TAO et al., *Proc. Natl. Acad. Sci. USA*, 90:8524-8528 (DtxR) (1993)

KELLY et al., *The Journal of Biological Chemistry*, 268(22)16781-16787 (A copper center of Cytochrome c oxidase) (1993)

Accordingly, when one of skill in the art tries to replace certain cysteine residues in a protein with other amino acid residues to give more stability to the protein, it is necessary to know:

- A. the position of cysteine residues in a protein;
- B. if the cysteine residue(s) is involved in disulfide bond; and

C. if the cysteine residue(s) constitutes an active center even though it is not involved in a disulfide bond.

Knowledge about B and C is very important. A cysteine residue which is involved in a disulfide bond cannot be replaced with other amino acid residue because disulfide bonds greatly affect the three dimensional structure of a protein. Therefore, it is only a cysteine residue not involved in a disulfide bond that may be replaced with another amino acid residue to give stability to a protein. However, as discussed above and as shown in the references attached hereto, in some cases, cysteine residues may constitute an active center of a protein even when the cysteine residues are not involved in disulfide bonds. It is therefore very important to know "C", i.e., if the cysteine residue constitutes an active center even though it is not involved in a disulfide bond.

Ushio and Okamura only provide information about A i.e., information about the position of cysteine residues in IL-18, but nothing about B and C in connection with IL-18.

On the other hand, in connection with IL-2 and IFN- β , information about A to C had been available. Mark, based on the available knowledge about A to C in connection with IL-2 and IFN- β , just replaced cysteine residues which had been known not to be involved in disulfide bonds and not to constitute an active

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center in IL-2 and IFN- β with using conventional genetic engineering method.

With regard to IL-18, information about B and C was not available and therefore it would not have been obvious how to successfully stabilize IL-18 by replacing specific cysteine residues.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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